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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,944	10/15/2003	Peter G. Schultz	54A-000610US	4561

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EXAMINER	
DESAI, ANAND U	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 08/31/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/686,944	SCHULTZ ET AL.	
	Examiner	Art Unit	
	Anand U Desai, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *26-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-57* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20040402*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-25, drawn to a method for synthesis of a glycoprotein, wherein an unnatural amino acid comprises an electrophilic moiety or a nucleophilic moiety, and a saccharide moiety comprises a nucleophilic moiety or an electrophilic moiety, classified in class 514, subclass 8.

II. Claims 26-34, drawn to a glycoprotein, classified in class 530, subclass 395.

III. Claims 35-45, drawn to a method for synthesis of a glycoprotein, the method comprising incorporating into a protein an unnatural amino acid that comprises a saccharide moiety, classified in class 530, subclass 333.

IV. Claim 46, drawn to a glycoprotein that contains an unnatural amino acid conjugated with a saccharide moiety, classified in class 436, subclass 87.

V. Claims 47-49, drawn to a host cell for synthesis of a glycoprotein, classified in class 435, subclass 325, 252.3, 419, and 254.2.

VI. Claims 50-54, drawn to a composition comprising a translation system comprising an orthogonal tRNA and an orthogonal aminoacyl tRNA synthetase, classified in class 435, subclass 74.

VII. Claim 55, drawn to a mutant synthetase polypeptide, classified in class 530, subclass 350.

VIII. Claim 56, drawn to an antibody, classified in class 530, subclass 387.1.

IX. Claim 57, drawn to a polynucleotide sequence encoding mutant synthetase, classified in class 536, subclass 23.1.

In claim 55, and 57, multiple sequences are set forth. Applicants must elect a single sequence they wish to be examined. This is not a species election. Rejoinder of all or a specified subset of the sequences is possible if Applicants provide a single and specific representative subsequence found in all or a specified subset of the sequences for search, and state that all or a specified subset of the sequences **are not patentable distinct**.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions I, III, and V are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are different methods of synthesis for glycoproteins. The different methods use different modes of operation to synthesis a glycoprotein. The different methods use different chemical compositions to synthesis a glycoprotein.

3. Inventions II, and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions use different chemical compositions to synthesis glycoproteins.

4. Inventions I and II are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the

glycoprotein of Invention II can be made by the materially different processes of Inventions I, III, and V.

5. Inventions III and IV are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the glycoprotein of Invention IV can be made by the materially different process such as solid phase synthesis.

6. Inventions VII, VIII and IX are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01).

The nucleic acids of Invention IX are related to the protein of Invention VII by virtue of encoding same. The DNA molecule has utility for the recombinant production of the protein in a host cell. Although the DNA molecule and protein are related since the DNA encodes the specifically claimed protein, they are distinct inventions because the protein product can be made by another and materially different process, such as by synthetic peptide synthesis. Further, the DNA may be used for processes other than the production of the protein, such as nucleic acid hybridization assay.

The proteins of Invention VII are related to the antibodies of Invention VIII by virtue of being the cognate antigen, necessary for the production of antibodies. Although the protein and antibody are related due to the necessary stearic complementarity of the two, they are distinct Inventions because the protein can be used in another and materially different process from the

use for the production of the antibody, such as in a pharmaceutical composition in its own right, or to assay or purify the natural ligand of the protein (if the protein is itself a receptor), or in assays for the identification of agonists or antagonists of the receptor protein.

The nucleic acid of Invention IX and the antibody of Invention VIII are related by virtue of the protein that is encoded by the nucleic acid and necessary for the production of the antibody. However, the nucleic acid itself is not necessary for antibody production and both are wholly different compounds having different compositions and functions. Therefore, these Inventions are distinct.

7. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

8. During a telephone conversation with Dr. Jonathan Quine on August 17, 2004 a provisional election was made without traverse to prosecute the invention of Group I, drawn to a method for synthesis of a glycoprotein, claims 1-25. Affirmation of this election must be made by applicant in replying to this Office action. Claims 26-57 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

9. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

10. Acknowledgment is made of applicant's claim for priority under 35 U.S.C. 119(e). The priority date is October 16, 2002.

Information Disclosure Statement

11. The information disclosure statement (IDS) submitted on April 2, 2004 is being considered by the examiner.

Specification

12. The disclosure is objected to because of the following informalities:

13. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. The hyperlinks are located on page 13, line 31, and page 51, lines 22, 27, and 31.

Appropriate correction is required.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1, 23-25 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 48, and 84 of copending Application No. 10/126,927 (US 2003/0082575 A1). Although the conflicting claims are not identical, they are not patentably distinct from each other because Schultz, P. et al. discloses a method of using a translation system with an orthogonal tRNA and an orthogonal aminoacyl tRNA synthetase to produce at least one protein comprising at least one unnatural amino acid.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 3, 9, 11, and 23-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

18. In claims 3 and 9, is the "keto" moiety a ketone moiety?

19. In claim 11, what are the "other reactants" required for glycosyltransferase activity?

20. The term "preferentially" in claim 23 is a relative term, which renders the claim indefinite. The term "orthoganol aminoacyl-tRNA synthetase" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Claims 24, and 25 are rejected for depending on a rejected claim.

21. In claim 25, a SEQ ID NO would remove the indefiniteness of the orthogonal tRNA, muttRNA$_{cua}$?

22. Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: In claim 1, the purification of a glycoprotein seems to be omitted. How does one know that a glycoprotein is synthesized unless it is purified? Claims 2-25 are rejected for depending on a rejected claim.

Claim Rejections - 35 USC § 102

23. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

24. Claims 1-7, 10-13, and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Rodriguez et al. (J. Org. Chem. 63(21): 7134-7135 (1998)). Rodriguez et al. disclose the method of synthesizing a glycoprotein. Rodrigues et al. synthesized carbohydrates bearing aminooxy, hydrazide, or thiosemicarbazide groups at their reducing termini and coupled these derivatives to ketone groups on a peptide scaffold (see Rodriguez et al. pp. 7134, 2nd paragraph). The glycoprotein was produced by coupling an unnatural amino acid with a reactive group and a saccharide with a reactive group. The peptide comprises an unnatural amino acid containing an electrophilic ketone group as the reactive group (see Rodriguez et al. pp. 7135, figure 1, structure 16, current application, claims 1, 2, 3). The nucleophilic carbohydrate derivative synthesized

was a functional analogue of the tetrasaccharide sialyl Lewis x (NeuAcα2->3Galβ1->4(Fucα1->3)GlcNac) (see Rodriguez et al. pp. 7134, Scheme 1, structure 9, current application, claims 1, 2, 5, and 10). The complex oligosaccharide was produced by using enzymatic methods involving α(2,3)-sailytransferase and the glycosyl donor CMP-sialic acid, and α(1,3)-fucosyltransferase with GDP-fucose as the glycosyl donor (see Rodriguez et al. pp. 7134-7135, 4th paragraph, current application, claims 11, 12, 13, and 21). The glycoprotein was produced by reacting the ketopeptide with the complex oligosaccharide (see Rodriguez et al. pp. 7135, 7th paragraph, current application, claim 1-7, 10-13, and 21).

Claim Rejections - 35 USC § 103

25. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

26. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

27. Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rodriguez et al. (J. Org. Chem. 63(21): 7134-7135 (1998)) in view of Palcic, M. (Methods in Enzymology,

230: 300-316 (1994)) and further in view of Kaushal, GP and Elbein, AD (Arch Biochem Biophys 250(1): 34-47 (1986), abstract). Rodriguez et al. disclose the method of synthesizing a glycoprotein. Rodrigues et al. synthesized carbohydrates bearing aminooxy, hydrazide, or thiosemicarbazide groups at their reducing termini and coupled these derivatives to ketone groups on a peptide scaffold (see Rodriguez et al. pp. 7134, 2nd paragraph). The glycoprotein was produced by coupling an unnatural amino acid with a reactive group and a saccharide with a reactive group. The peptide comprises an unnatural amino acid containing an electrophilic ketone group as the reactive group (see Rodriguez et al. pp. 7135, figure 1, structure 16, current application, claims 1, 2, 3). The nucleophilic carbohydrate derivative synthesized was a functional analogue of the tetrasaccharide sialyl Lewis x (NeuAcα2->3Galβ1->4(Fucα1->3)GlcNac) (see Rodriguez et al. pp. 7134, Scheme 1, structure 9, current application, claims 1, 2, 5, and 10). The complex oligosaccharide was produced by using enzymatic methods involving α(2,3)-sailytransferase and the glycosyl donor CMP-sialic acid, and α(1,3)-fucosyltransferase with GDP-fucose as the glycosyl donor (see Rodriguez et al. pp. 7134-7135, 4th paragraph, current application, claims 11, 12, 13, and 21). The glycoprotein was produced by reacting the ketopeptide with the complex oligosaccharide (see Rodriguez et al. pp. 7135, 7th paragraph, current application, claim 1-7, 10-13, and 21). Rodriguez et al. further describes the majority of current methods for attaching a sugar to peptide scaffolds involves the coupling of electrophilic carbohydrate derivatives with a peptide containing a nucleophilic moiety (see Rodriguez et al., pp. 7134, 2nd paragraph, current application, claims 8, 9). Rodriguez et al. does not teach using the particular glycotransferases, β-1,4-galactosyltransferase and β1-4N-acetylglucosaminyltransferase, in the synthesis of defined oligosaccharide structures. Palcic, M.

discloses various glycosyltransferases, particularly β-1,4-galactosyltransferase and β1-4N-acetylglucosaminyltransferase, and their use in the synthesis of defined oligosaccharide structures (see Methods in Enzymology, 230: 300-316 (1994), entire document, particularly table 1, current application, claims 14, 15). Kaushal, GP and Elbein, AD disclose purification of a β-mannosyltransferase enzyme that uses GDP-mannose to form Man-β-GlcNAc-GlcNAc-pyrophosphoryl-dolichol (see Kaushal, GP and Elbein, AD (Arch Biochem Biophys 250(1): 34-47 (1986), abstract, current application, claims 16-20). It would have been obvious to person having ordinary skill in the art to use the various glcyotransferases to produce particular oligosaccharide structures to synthesis glycoprotein conjugates. One would have been motivated to make various glycoprotein conjugates because of the growing realization that glycoconjugates participate in a wide range of normal and pathophysiological processes. Therefore, it would have been obvious to the person having ordinary skill in the art to use various glycosyltransferases, to produce a complex oligosaccharide moiety to examine the function of various glycoconjugates (current application, claims 1-21).

28. Claims 1-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rodriguez et al. (J. Org. Chem. 63(21): 7134-7135 (1998)) in view of Palcic, M. (Methods in Enzymology, 230: 300-316 (1994)) and further in view of Kaushal, GP and Elbein, AD (Arch Biochem Biophys 250(1): 34-47 (1986), abstract) as applied to claims 1- 21 above, and further in view of Wang, L. et al. (Science 292: 498-500 (2001)). Wang, L. et al. discloses the incorporation of unnatural amino acids into proteins using orthogonal tRNA and an orthogonal tRNA synthetase. Wang, L. et al. demonstrate the incorporation of the unnatural amino acid, O-methyl-L-tyrosine,

into the dihydrofolate reductase protein with a fidelity rivaling that of the natural amino acids (see Wang, L. et al., pp. 499, particularly figure 2). The ability to introduce novel amino acids into proteins is suggested to provide a new tool to study protein and cellular function (see Wang, L. et al., pp.500, last paragraph). One would have been motivated to make various glycoprotein conjugates because of the growing realization that glycoconjugates participate in a wide range of normal and pathophysiological processes. Therefore, it would have been obvious to the person having ordinary skill in the art to use the orthogonal tRNA/tRNA synthetase to introduce unnatural amino acids conjugated with reactive groups that can be covalently bound to carbohydrate structures (as disclosed Rodriguez et al.) to make synthetic glycoproteins (current application, claims 1-25).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U Desai, Ph.D. whose telephone number is (571) 272-0947. The examiner can normally be reached on Monday - Friday 9:00 a.m. - 5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (517) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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August 23, 2004

Karen Cochrane Carlson PhD

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER